UPPER GASTROINTESTINAL BLEED: A COMPARATIVE OUTCOMES STUDY OF PRE AND POST IMPLEMENTATION OF MANAGEMENT GUIDELINES IN THE ACUTE CARE SURGERY UNIT, GROOTE SCHUUR HOSPITAL

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ABSTRACT

Background: Upper gastrointestinal bleeding (UGIT) is a common presentation to hospital and can result in a significant morbidity, mortality and hospital costs. Consensus guidelines are present from various international expert bodies regarding the management of these patients and compliance with these guidelines is variable and is dependent on rigorous implementation and continuous audits.

Aim: The primary aim of this study is to evaluate complaints to three aspects of management of UGITB (time of endoscopy ,use of dual endotherapy and haemoglubin trigger for transfusion) at Acute Care Surgery Unit, at Groote Schuur Hospital.

Methods: This is a comparative study between a retrospective control group and a prospective cohort post implementation of a quality improvement program (QIP).

Results: This study included 109 patients, 51 in the control and 58 in the QIP group. The two groups were statistically comparable in terms of demographics, clinical presentation, referral pattern and endoscopy finding.

Over 80% in both groups had their endoscopy within 24 hours (Control 83.7%, QIP 81.6%). Time to endoscopy was not statistically significantly different between the Control and QIP groups for low and high-risk patients ((suspected varices or Modified Glasgow-Blatchford Score (MBS) >10)). However, when both groups are combined, patients with an MBS of >10 or more had a statistically shorter 'Time to scope' by 8 hours than those with a score < 10 (p=0.02).

In the presence of blood in the upper GIT on OGD, the practice of dual endotherapy improved post-implementation (p=0.023). Out of 12 bleeding ulcers (Forrest IA, IB, and IIA, IIB) 5 (41.6%) had dual therapy in the Control group versus 10 out of 14 (71%) in QIP group.

Blood transfusion was performed in (Control 72.5%, QIP 65.5%). The mean Haemoglobin in stable patients who were transfused was statistically different between Control 6.3 (SD±2) and QIP 5.7 (SD±1.69) (p=0.04). The number of transfusions for HB above 7 was 12 (23.5%) (Control) to 6 (10.3%) (QIP) (p=0.047). Thirty-day mortality rate was 9.8% (Control) and 10.3% (QIP). The QIP did not affect re-bleeding, surgery and mortality.

Conclusion: This QIP was successful in terms of using dual endotherapy for high-risk ulcers and decreasing the rate of inappropriate blood transfusions. The time to endoscopy did not significantly change between the two groups; however, the 24h endoscopy rate was over 80%, which is better than high-income countries registry audits.

(Abstract words count 384)

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1. Literature review

1.1 Introduction

Upper gastrointestinal bleed (UGIT) is a common emergency presentation that can lead to hemodynamic compromise and mortality. Anatomically, frank blood loss proximal to the ligament of treitz is considered as an UGIT bleed.[1] The incidence is reported as 48 to 172 per 100000 in first world literature.[2 3 4 5] Various international consensus guidelines are available to aid triage and management. The mortality rate has decreased significantly after the 1990s. This is attributed to the availability of proton pump inhibitors and advances in endoscopic management. However, the decrease in mortality has plateaued in most countries, currently reported between 2 to 14%.[3 6 4 7] It is hoped that strict implementation of consensus guidelines can further improve mortality rates.

1.2 Incidence

The incidence of UGIT bleed in South Africa is not known. Internationally the figures vary from 48 to 172 per 100000 patients.[2 7 5] In the United Kingdom this translates to 50 000 to 70 000 hospital admissions yearly with about 4000 deaths.[7] A Japanese population study showed that death related to peptic ulcer disease has not declined after 1990 despite advances in treatment.[8]

1.3 Etiology and risk factors

UGIT bleed can be broadly categorized into variceal bleeding (VB) and non-variceal bleeding (NVB). NVB predominates in 80 to 90% of cases. Peptic ulcer disease (PUD) accounts for 20 to 50% of NVB. Helicobacter pylori infection and the use of non-steroidal anti-inflammatory drugs (NSAIDs) have strongly been associated with PUD. A meta-analysis by Huang et al showed that the relative risk of a bleeding ulcer with H. Pylori was 1.79, with NSAID use was 4.85 and combined was 6.13.[9] Similarly, in a study by Papatheodoridis et al, *H.* pylori were detected more in cases of bleeding than controls and double the risk of UGIT bleeding amongst NSAIDs

users.[10] The incidence of PUD ulcer bleed has decreased in younger patients and increased in the older patient population group. This is most likely due to the increasing use of low dose aspirin as prophylaxis in the older population. The number of older patients with bleeding PUD increased from 9.2% in the 1970s to 27.8% in the 1990s.[8]

Portal hypertension secondary to cirrhosis is the leading cause of variceal bleeding. Alcoholic cirrhosis is the dominant etiology for portal hypertension.[11 12 13] The cumulative incidence of varices in cirrhotic patients at 10 and 20 years were 44% and 53% respectively.[14]

Table 1: Causes of Upper Gastrointestinal bleeding

Causes	Percentage (%)
Common Causes	
PUD	20-50
Mallory-Weiss tear	20-25
Sever erosive gastroduodenitid/ esophagitis	10-15
Esophageal varices	
Portal hypertensive gastropathy	
Angiodysplasia (vascular ectasia)	5
Mass lesions (polyps/cancer)	1-2
No lesion identified	10-15
Less common causes	
Dieulafoy's lesion	
Gastric antral vascular ectasia	
Hemobilia	
Hemosuccus pancreaticus	
Aortoenteric fistula	
Cameron lesions	
Ectopic varices	
Iatrogenic bleeding after endoscopic intervention	

**only known percentage prevalence is shown in the table*

1.4 Clinical picture

Upper GI bleeding can present with a wide variety of signs and symptoms depending on the speed of the bleed. The most indolent form may present with anemia with its myriad of symptoms like fatigue, dizziness, and pallor. The acute form present with haematemesis (vomiting of blood, which may be bright red or has an appearance of ground coffee) with or without melena (passage of dark tarry stools). Patients with rapid blood loss can present with hemodynamic shock and require urgent attention and intervention to prevent mortality. Up to 10% of upper GI bleeding patients have hematochezia (passage of fresh blood in the feces), and can present with signs and symptoms of hypovolemic shock.[15]

Re-bleeding in prospective trials is often defined as evidence of fresh bleeding with hypovolemic shock or a decrease in Hb of $\geq$ 2g/dl over 24-hours, with confirmation of recurrent bleeding by endoscopy or surgery.[16] This is especially high in variceal bleeding (25–29%) and peptic ulcer bleeding (20–22%). [5]

1.5 Resuscitation

This literature review will focus on certain parts of management only. For the purpose of the study, we decided to implement certain aspects of management that we think we are poor at and could make a difference in outcomes. These aspects will be discussed in this literature review more thoroughly.

Initial management should focus on resuscitation corresponding to a hemodynamic status. This is done using the ATLS® principles. Volume restoration initially is done using a crystalloid or colloid. In patients known with or suspected to have liver cirrhosis, the use of Saline solution should be avoided or limited. The lack of aldosterone metabolism by failing liver results in the retention of sodium and hence water. The excess fluid can result in worsening ascites, which increases the risk of spontaneous bacterial peritonitis. Sepsis will result in liver decompensation, increasing portal pressures and worsening coagulopathy. Re-bleeding as a result of decompensation has a mortality rate of above 70%.[12 17]

1.6 Blood transfusion

Blood and blood products are used either during resuscitation or to correct anemia in stable patients. Hb thresholds for transfusion in UGIB remain controversial. The threshold recommended in non-variceal bleeding (NVB) is a Hb level of <7 g/dL and for VB <8 g/dL.[18 19] In patients with ischemic heart disease (IHD) or risk, the Hb target should be 9g/dL. A RCT published in the New England Journal of Medicine in 2013 shows that restrictive transfusion strategy (Hb < 7g/dL) had better mortality outcomes. The subgroup that performed best was patients with variceal bleeding with Child-Pugh score A and B. Re-bleeding and adverse effects were higher in the liberal strategy group. This transfusion trigger of Hb 7, however, should only be applied in the correct clinical setting i.e. out of resuscitation scenario and stable patients without IHD.

1.7 Risk stratification assessment:

Risk stratification scores are used to triage patients after resuscitation, which helps with identifying the high risk group that needs earlier intervention and closer monitoring. There are pre and post endoscopy scores. All consensus guidelines recommend using scores to stratify patients into low and high risk. However, registry data worldwide shows poor use of these scores. [20]

Initial risk stratification is important in determining the timing of endoscopy. The Modified Blatchford score and Rockall pre-endoscopy score can be used to identify patients who require endoscopic intervention earlier. The full Rockall score includes endoscopic findings and is used to predict re-bleeding and mortality.[4 2]

MBS of 0 and 1 has a less than 1% chance of needing intervention and these patients can be considered for outpatient management. Patients with MBS score of 10 or more are likely to need urgent intervention compared to patients with lower scores.

The full Rockall score can be done post endoscopy to identify patients at risk of re-bleeding and higher mortality. A score of less than 2 has zero mortality. A score of 3 to 4 implies medium risk with re-bleeding rate of up to 14% and mortality of up to 5.3%. A score of 5 and above implies high risk. Patients with the highest score of 7 have a re-bleeding rate of 41.8% and mortality of 41%. 4

A new score, AIMS 65 score has been validated as another pre-endoscopic risk assessment tool. It consists of clinical and biochemical variables like albumin (< 30 g/L), INR > 1.5, mental state alteration, Systolic BP < 90 and age > 65. It seems superior to pre-endoscopic Rockall and Blatchford scores in predicting inpatient mortality, length of stay, and need for intensive care admission.21 A low score of 1 or less has a mortality rate of 3.2% and the highest score of 5 has a mortality rate of 24.5%. It was not possible to do this score with our study as not all patients have an albumin and INR checked in our cost saving system. We also decided to use the Modified Blatchford score as it requires less data and has been validated to be equally efficient as the full or Glasgow – Blatchford score.

For patients with liver cirrhosis we also used the Child Pugh score. Please see Addendum for all above mentioned scores. (With the tables please put MBS, Rockall pre and post, and child Pugh score).

1.8 Pharmacological therapy

A) Proton Pump Inhibitors

Acid suppressants allow the gastric pH to rise resulting in a more favorable condition for clot formation and stabilization. Proton pump inhibitors (PPIs) are superior to H2 Antagonists and placebo for down staging lesions with a high stigma of bleeding and therefore less endoscopic intervention is necessary. However, this does not translate to improved survival, less surgery or less re-bleeding when given pre-endoscopy. A 2010 Cochrane review, 22 23 and other studies like the meta-analysis by Andriulli et al amongst others supports this finding.16 24 25

In the South African context where endoscopy is not readily available at all facilities or after hours even in bigger centers, the commencement of IV PPI is beneficial.

The best route and dosage of PPI is not clear. NICE recommends routine administration of PPI for NV UGIB and signs of recent hemorrhage shown at endoscopy but does not recommend the best route, dosage or duration.[7] In western countries it is standard practice to give high dose PPI followed by an infusion for 48 to 72 hours for patients with lesions with high stigmata of bleeding (Forrest IA, IB, IIA, and IIB). There are no good head to head trials comparing high dose to low dose or to oral treatment. However, in one study low dose IV PPI did reduce re-bleeding rates but didn't impact mortality or surgery need.[26] When IV treatment is not available, oral PPIs should be given at four times higher dose.[27]

B) Tranexamic acid

The use of Tranexamic acid (TXA), an anti-fibrinolytic drug, in UGIT bleed has been found to be beneficial. A meta-analysis of RCTs in patients with UGIT bleed showed a 39% reduction in mortality in patients that were given TXA than in the control group.[28] This is not routine practice in our center or found to be in the large registry data published internationally.

C) Vasopressors

There is good evidence to support the use of vasoactive drugs to lower portal pressures for patients with variceal bleeding. Terlipressin (a synthetic vasopressin analogue) in placebo controlled trials has shown to increase the success of endoscopic management and decrease mortality.[29] Somatostatin or its analogue Octreotide have shown similar efficacy to terlipressin in a meta-analysis.[30 31]

D) Antibiotics

Antibiotic prophylaxes for gram- negative organisms has been shown to improve survival after variceal bleeding. A 2010 review summarised that prophylactic antibiotic use decreased infection and mortality rates.[32]

1.9 Endoscopic management

A) Early diagnostic endoscopy

Endoscopy remains an essential tool for the assessment and treatment of UGIT bleeding. Endoscopy done within 24 hours of admission is considered to be early. Most guidelines currently advocate that patients who are hemodynamically stable and have no signs of ongoing bleeding after initial resuscitation should have an endoscopy within 24 hours.[7 18] Large registry analysis shows variable adherence to early endoscopic guidelines. In the Canadian RUGBE cohort, 76% of endoscopy was performed under 24 hours from admission with a mean of 23 hours.[3] In the United Kingdom only 50% had endoscopy within 24 hours.[33] Comparing very early (<12 hours) to late early (>12 hours) endoscopy, a meta-analysis found no significant reduction in re-bleeding, surgery or mortality with early (<12 hours) endoscopy compared with late (>12 hours) endoscopy.[34 35 36 37]

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Moreover, it was found that urgent endoscopy (0 to 8 hours) versus early endoscopy (6 or8 to 24 hours), did not show difference in clinical outcomes.[36 38 39]

Early endoscopy (<24 hours) decreases hospital stay, is cost effective and safe in terms of discharging appropriately once endoscopy is done compared to endoscopy after 24 hours. Very early endoscopy (<12 hours) is recommended in certain risk groups like the suspected variceal bleed or NVB with high MBS (>10). VB is likely to recur and hence early endoscopy and treatment prevents re-bleeding and mortality. A high MBS (>10) indicates severe bleeding, these patients are likely to have ongoing bleeding or are at high risk of re-bleeding.

B) Second look endoscopy

Current data does not recommend second look endoscopy. In the era of dual endotherapy and use of high dose PPI for high-risk lesions there is no benefit from a second look endoscopy.[40 41] [27]This should be reserved for patients showing signs of ongoing bleeding.[18]

C) Therapeutic endoscopy

The modified Forrest classification is used to stratify bleeding ulcers which can aid treatment decision and risk stratification for re-bleeding and mortality. (addendum ,Forrest classification) All actively bleeding or ulcers with stigmata of recent bleed (Forrest I and 2A) need endoscopic intervention. [4]

D) Therapeutic endoscopy for non-variceal bleeding

Various modalities of endotherapy can aid hemostasis, including injection, application of mechanical clips, and thermal therapy.

1) **Injection therapy**:

The injection of adrenalin in non-variceal bleeding is based on the principle of vasoconstrictive action and vascular tamponade, fibrinoid degeneration of the arterial wall and thrombus formation. In a large meta-analysis of 1,673 patients, additional therapy to adrenalin injection reduced the re-bleeding rate from 18.4% to 10.6%, and mortality from 5.1% to 2.6%.[42]

2) **Mechanical therapy:**

Endoclips or hemoclips are used for hemostasis for bleeding vessels. A meta-analysis showed clip application was shown is better than injection therapy in achieving definitive hemostasis (86.5% vs 75.4%).[43]

3) Thermal therapy:

Two types of thermal hemostasis are available: contact and non-contact. With contact thermal therapy, the vessel is sealed by a combination of mechanical pressure and heat, causing coagulation and thrombosis. Non-contact thermal therapy includes argon plasma coagulation (APC), where ionized argon gas delivers a monopolar electrical current coagulating tissues.[44]

E) Therapeutic endoscopy for variceal bleeding

Variceal bleeding can be controlled with various methods including injection sclerotherapy or tissue adhesive injection, band ligation and Sengstaken tube insertion.

1) Injection therapy:

Sclerosant agents (tetrcyadel sodium, sodium morrhuate, and ethanolamine oleate) are injected in or next to varices necrosis, fibrosis and obliteration of the varices. Complications include severe esophagitis, esophageal stricture formation and oesophageal perforation.[12]
Tissue adhesives (cyanoacrylate tissue adhesives such as N-butyl-cyanoacrylate (histoacryl), isobutyl-2-cyanoacrylate, or 2-octyl cyanoacrylate) are used for gastric varices. In a retrospective study, thirty-seven patients underwent cyanoacrylate glue injections. It was found that initial hemostasis was achieved in 95%, while early rebleeding occurred in 8% and late rebleeding occurred in 28% of patients.[45]

1) Mechanical therapy:

Band ligation is the recommended endoscopic treatment of oesophageal varices. [17 46 26]
Band ligation results in better hemostasis and less mortality compared to sclerotherapy. [47] For gastric varices glue injection is superior to banding.[48]

2) Balloon tamponade:

Balloon tamponade is useful when there is a failure of other methods of variceal hemostasis. Sengstaken- Blakemore tube achieves hemostasis in 91.5% of cases, with a recurrence of bleeding in approximately 50% of cases after balloon deflation. It is a temporary method to stabiles patient and used as a bridge to a more definitive procedure. [49]

F) Dual therapy

A meta-analysis of injection therapy versus injection with the second modality showed less re-bleeding with dual therapy (10.6% versus 18.4%) and less mortality (2.6% versus 5.1%). Further studies and a Cochrane review have confirmed that injection therapy on its own is inferior to dual therapy. All consensus guidelines currently recommend dual therapy for ulcers with high stigmata of bleeding (Forrest I and 2A).

G) Adherent clot

There is controversy regarding the management of an adherent clot (Forrest 2b ulcer). The risk of re-bleeding varies from 8 to 36% with clot manipulation. Clot irrigation or endoscopic manipulation can reveal a higher stigmata lesion underneath in 70% of patients. [50] Two meta-analysis of RCTs showed no benefit with endoscopic management versus high dose IV PPI. [26] Another analysis of 4 trials showed less re-bleeding with endoscopic management. A meta-analysis by Kahi et al showed less re-bleeding and need for surgery, however, this did not impact mortality. [51] Consensus guidelines recommend either option, endoscopic treatment or higher dose IV PPI.

1.10 Outcomes and predictors of mortality

Various studies have found certain factors to be associated with increased mortality. The risk stratification scores for UGIT bleed factors these predictors to identify patients at risk of needing more urgent treatment and patients with higher mortality risk. Mortality after UGIT bleed has been quoted as between 2 and 14% in the literature. [6 2 7 3 52 4]

The Italian PNED registry showed that advanced age (>80); severe co-morbidities like ASA >3, renal failure, liver failure, and advanced malignancy; low Hb (<7g/dL) and failure of endoscopic treatment (re-bleeding) were all factors associated with mortality. This registry's mortality rate was 4.5%. [52]

The Canadian RUGBE study had a mortality rate of 5.4%. This is less than previously reported and it is attributed to the use of proton pump inhibitors.[3]

Rockall et al's landmark paper notes re-bleeding as a major risk factor for mortality. They noted that patients in the middle score group (Rockall 3-4) had a fivefold increase in mortality with re-bleeding and patients with higher scores (above 5) had a threefold increase in mortality with re-bleeding. There was zero mortality in the group with scores 2 and less. The overall mortality in this paper was 14%.

Levin et al's study done at our hospital previously showed a mortality rate of 12.8%. Re-bleeding and presence of co-morbid disease were found to be significant risk factors for mortality. [53]

A new prognosticator score, AIM65 includes low albumin levels (<30g/L), as it has been shown to be an independent predictor of mortality.[54]

Other risk factors are shock, clinical evidence of bleeding and sepsis.

A study by parvez et al in a private tertiary state of the art hospital in India showed a mortality rate of 2.6%. They attribute this low rate to expedited endoscopy, availability of critical care and early presentation to hospital by the patients.[6]

1.11 Guideline recommendations and practice

International guidelines for the management of UGIT are constantly being refined by senior gastroenterologists as evidence from RCT and cohort studies have accrued to provide sound evidence on which to base their recommendations. There are various guidelines from several countries available like NICE UK and American College of Gastroenterology Guidelines for upper GIT bleeding.

The international consensus recommendations on the management of patients with Non variceal UGIT bleeding from 2010 contains 11 recommendations in six categories and details the criteria and cut-off levels when appropriate. These categories are: Adequate resuscitation, prognostic stratification, transfusion triggers, PPI acid suppression, early endoscopy and dual endotherapy.[19]

Pertinent points of recommendations from the International consensus document in relation to our study are :[19]

1) Resuscitate appropriately after initial evaluation
2) Use prognostic scales to risk stratify into low and high risk for re-bleeding and mortality
3) Transfuse blood if Hb $\leq$7g/dL in stable patients
4) Consider pre-endoscopic proton pump inhibitor (PPI) to downstage lesion
5) Early endoscopy (<24 hours) is recommended
6) Adrenalin injection therapy alone is suboptimal and should be used in conjunction with another method
7) Finding a clot in the ulcer bed warrants targeted irrigation to dislodge the clot, with appropriate therapy of underlying lesion
8) Adherent clot management is controversial. Endoscopic therapy or intensive PPI therapy alone may suffice

9) Clips, thermocoagulation or sclerosant injection can be used in high risk lesions, alone or in conjunction with adrenalin injection
10) Routine second look endoscopy is not recommended and reserved for re-bleeding
11) An intravenous bolus with continuous infusion of PPI should be used after successful endoscopic therapy of high risk ulcers

Audits of registries show mostly below average uptake of guidelines. There is definitely a gap between what is recommended and what happens in real practice. In the United Kingdom there was 47.5% to 66% compliance to endoscopy within 24 hours in baseline audits.[55 56] Canadian RUGBE study showed a 76% 24 hour endoscopy rate.[3] Similarly to the French audit [57] in 2006 showed that 70.9% had injection therapy alone for high-risk bleeding ulcers and mirrored our own institutions practice of a 100% monotherapy use for high risk ulcers reported by Levin et al between 2004 and 2009.[53]

1.12 The GSH perspective

The GSH endoscopy service is fragmented and variable. The service is provided by the GI unit during office hours, which comprises of surgical gastroenterology, acute care surgery and Medical GIT consultants, fellows and registrars. After-hours the unit is not available, and all endoscopy must be done in theater. With aging equipment, confusion about who is buying consumables and a mixed rotation for endoscopy cover, the care were dependent on the skills and enthusiasm of the on-call team. The last few years with acute care surgery being at the forefront of emergency cover, they have addressed all the hurdles for after-hour endoscopy. The study was done after they ensured equipment availability (it is still not ideal circumstances), adequate supply of consumables, availability of Gold probe™ in theater and change of on-call roster to avoid confusion (All after-hours endoscopy now provided by Acute care surgery only). Standard management protocols for management of UGIT bleed were drawn up and implemented as part of the project. They felt the areas they did poorly were the

delay to endoscopy after admission and use of adequate dual endotherapy for bleeding ulcers. Blood transfusion protocol out of resuscitation was also not standardized. These three points are the focus of this quality improvement program. They also aim to audit their mortality over this two-year period.

1.13 Conclusion

UGIT bleeding is a common emergency admission. The mortality rate has decreased significantly with the use of high dose PPI and adequate endotherapy in first world countries. Adherence to consensus guidelines remains problematic everywhere. Can mortality rates drop even more with strict implementation of these guidelines? Is it possible to adhere to these guidelines in a system that has its challenges?

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2. PUBLICATION-READY MANUSCRIPT

2.1 Title page

UGIT bleed: A comparative outcomes study of pre and post implementation of management guidelines in the Acute Care Surgery Unit, Groote Schuur Hospital

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2.2 ABSTRACT

Background: Upper gastrointestinal bleeding (UGIT) is a common presentation to hospital and can result in a significant morbidity, mortality and hospital costs. Consensus guidelines are present from various international expert bodies regarding the management of these patients and compliance with these guidelines is variable and is dependent on rigorous implementation and continuous audits.

Aim: The primary aim of this study is to evaluate complaints to three aspects of management of UGITB (time of endoscopy ,use of dual endotherapy and haemoglubin trigger for transfusion) at Acute Care Surgery Unit, at Groote Schuur Hospital.

Methods: This is a comparative study between a retrospective control group and a prospective cohort post implementation of a quality improvement program (QIP).

Results: This study included 109 patients, 51 in the control and 58 in the QIP group. The two groups were statistically comparable in terms of demographics, clinical presentation, referral pattern and endoscopy finding.

Over 80% in both groups had their endoscopy within 24 hours (Control 83.7%, QIP 81.6%). Time to endoscopy was not statistically significantly different between the Control and QIP groups for low and high-risk patients ((suspected varices or Modified Glasgow-Blatchford Score (MBS) >10)). However, when both groups are combined, patients with an MBS of >10 or more had a statistically shorter 'Time to scope' by 8 hours than those with a score < 10 (p=0.02).

In the presence of blood in the upper GIT on OGD, the practice of dual endotherapy improved post implementation (p=0.023). Out of 12 bleeding ulcers (Forrest IA, IB and IIA, IIB) 5 (41.6%) had dual therapy in the Control group versus 10 out of 14 (71%) in QIP group.

Blood transfusion was performed in (Control 72.5%, QIP 65.5%). The mean Haemoglobin in stable patients who were transfused was statistically different between Control 6.3 (SD±2) and QIP 5.7 (SD±1.69) (p=0.04). The number of transfusions for HB above 7 was 12 (23.5%) (Control) to 6 (10.3%) (QIP) (p=0.047). Thirty day mortality rate was 9.8% (Control) and 10.3% (QIP). The QIP did not affect re-bleeding, surgery and mortality.

Conclusion: This QIP was successful in terms of using dual endotherapy for high risk ulcers and decreasing the rate of inappropriate blood transfusions. The time to endoscopy did not significantly change between the two groups; however the 24h endoscopy rate was over 80%, which is better than high income countries registry audits.

(Abstract word count 384)

2.3 Text of article

Introduction and background

Upper gastrointestinal (UGIT) bleeding is a common reason for hospital admission that carries a significant risk of morbidity and mortality. The reported incidence varies from 48 to 172 per 100000 in high-income countries.[1 2 3 4] In the last two decades the mortality rate has decreased and currently ranges between 2 and 14%.[5 6 3 7] The only recent publication from South Africa was by Levin et al in 2012. This tertiary care unit study reported a mortality rate of 12.8% and surgery rate of 7.9% for non-variceal haemorrhage in 227 patients over 6 years.[8]

Management has evolved with adjunct therapies and technical refinements in endotherapy and has resulted in a variety of consensus guidelines designed to improve the management and outcomes of these patients. Various analysis of compliance to these guidelines suggests that these are not rigorously implemented.[9 10] Against this background we wished to examine our compliance with regards to our own internationally adapted guidelines, in the management of patients with UGIT bleeding, before and after the implementation of a quality improvement program, in a tertiary referral unit.

Materials and Methods

Retrospective data collected on 51 consecutive patients over a year constituted the control group. Data on 58 consecutive patients were collected prospectively in a year, following the Quality improvement program (QIP) implementation. This program consisted of dissemination of a unit protocol via email, lectures and placement of protocol posters at strategic points. The target intervention groups were General surgery and Medical Gastroenterology registrars, fellows and, consultants who are involved in the care of UGIT bleeding patients. A customized redcap database was developed to collect data. The study protocol was approved by the local Human research ethics committee (244/2017)

All patients admitted to acute care surgery, Groote Schuur hospital (GSH) with signs and symptoms of UGIT bleeding were included in this study. Patients that demised prior to

endoscopy (unconfirmed) or had no blood or cause for UGIT bleeding at endoscopy were excluded from this study. GSH is a tertiary referral institution which admits UGIT bleeding from its own catchment area and is the referral hospital for three secondary level hospitals that have variable ability to provide a 24-hour endoscopy service. GSH provides a 24 hour endoscopy service in a dedicated endoscopy unit during working hours (8 am-4 pm weekdays) with after-hours endoscopy being performed in the operating theatre. Patients who presented with Grade III shock (SBP < 100, HR >120) were deemed unstable. All patients were risk-stratified using the Modified Blatchford Score (MBS), a validated scoring system that incorporates initial clinical findings; blood pressure, heart rate, Hb and urea. Post endoscopy Rockall score parameters were recorded to identify patients at risk of re-bleeding and death. Child-Pugh score was used to assess the severity of liver decompensation in variceal bleeding. The policy is to give a stat dose of intravenous proton pump inhibitor (PPI) to high-risk patients at admission and to continue as indicated by endoscopy findings. Regards to suspected variceal bleeding, our policy is to start Octreotide infusion on admission.

The Quality improvement program focused on aspects of UGIT bleed care we perceived as being poorly adhered to at our institution. We compared adherence to the recommendations between the two cohorts for: time to endoscopy (within 24 hours from admission for all, and <12 hours for suspected variceal haemorrhage and a MBS>10), the use of dual-modality endotherapy and blood transfusion related to a haemoglobin trigger of <7g/dL in hemodynamically stable patients with no ischemic heart disease. The primary aim of this study was to evaluate the compliance of these three parameters as defined in our guidelines, pre and post QIP and their comparison with to international data. Secondary aims were to assess if the implementation of QIP affected re-bleeding, surgery and mortality rates.

Results

This study included 109 patients, 51 in the control and 58 in the QIP group. The baseline characteristics of the two groups are shown in Table 1. The majority of the characteristics were similar between the two groups except for aspirin usage which was significantly higher in the control group.

The mean age for both groups was 55 years of age. The frequency of referrals from secondary level hospitals was similar in the two groups. The reason for referral was unavailability of scope adjuncts for adequate dual therapy or banding (Control 76.2%, QIP 75%) and unavailability of after-hours endoscopy service (Control 23.8%, QIP 25%). The majority of the patients were normotensive on arrival and Grade III shock was present in 20% of both groups. The frequency of co-morbidities was equally distributed in both groups. The most common co-morbidities were smoking, non-steroidal use and chronic liver disease. Historical evidence of bleeding was twice as common for hematemesis as for melena in both groups. However, melena was more frequently confirmed on examination than hematemesis.

The MBS prior to endoscopy was 8.6 (SD $\pm$4.2) in the Control group and 8.3 (SD $\pm$3.1) in QIP group. Post endoscopy Rockall score showed a mean of 3.45 for Control and 3.54 for QIP groups. There was no statistical difference between the two groups.

Table 1: Comparison of demographic and baseline characteristics for the Control and QIP groups

VARIABLE		CONTROL	QIP	P VALUE <0.05
DEMOGRAPHICS AND REFERRAL PATTERN				
TOTAL		51	58	
AGE MEAN (RANGE)	Mean (SD)	55 (17.1)	55 (15.6)	
MALE	N (%)	31 (60.8)	35 (60.3)	
FEMALE	N (%)	20 (39.2)	22 (37.9)	
REFERRALS: SECONDARY HOSPITAL	N (%)	20 (39.2)	18 (31.0)	
REFERRAL: INPATIENT	N (%)	3 (5.9)	10 (17.2)	
EMERGENCY UNIT ADMISSION	N (%)	31 (60.8)	39 (67.2)	
AFTER HOURS ADMISSION	N (%)	36 (70.5)	34 (58.6)	
ADMISSION CLINICAL PARAMETERS				
SYSTOLIC BLOOD PRESSURE (MMHG)	Mean (SD)	121 (26.2)	116 (23.8)	
HEART RATE (BPM)	Mean (SD)	98 (16.3)	102 (20.3)	
HEMOGLOBIN (G/DL)	Mean (SD)	7.36 (3.06)	7.01 (2.65)	
GRADE II SHOCK	N (%)	17 (33.3)	19 (32.7)	
GRADE III SHOCK	N (%)	11 (21.5)	13 (22.4)	
UPPER TRACT BLEEDING EVIDENCE				
MALENA CONFIRMED	N (%)	25 (49.0)	34 (58.6)	
MALENA HISTORY	N (%)	17 (33.3)	18 (31.0)	
HEMATEMESIS CONFIRMED	N (%)	3 (5.9)	8 (13.8)	
HEMATEMESIS HISTORY	N (%)	31 (60.8)	39 (67.2)	
FRESH BLOOD SEEN ON SCOPE	N (%)	6 (11.7)	12 (20.6)	
OLD BLOOD SEEN ON SCOPE	N (%)	16 (31.3)	19 (32.7)	
RISK FACTORS AND CO-MORBIDITIES				
SMOKER	N (%)	24 (47.0)	25 (43.1)	
NSAIDS	N (%)	18 (35.3)	15 (25.8)	
ASPIRIN PROPHYLAXIS	N (%)	11 (21.5)	3 (5.1)	0.04
PREVIOUS UGIT BLEED	N (%)	11 (21.5)	16 (27.6)	
WARFARIN	N (%)	2 (3.9)	2 (3.4)	
ISCHEMIC HEART DISEASE	N (%)	6 (11.7)	6 (10.3)	
CARDIAC FAILURE	N (%)	6 (11.7)	1 (1.7)	
CHRONIC RENAL FAILURE	N (%)	3 (5.9)	0(0)	
LIVER DISEASE	N (%)	12 (23.5)	16 (27.5)	
RISK STRATIFICATION				
MODIFIED BLATCHFORD SCORE	Mean (SD)	8.6 (4.2)	8.3 (3.1)	

ROCKALL SCORE (POST ENDOSCOPY)	***Mean (SD)***	***3.45 (1.8)***	***3.54 (1.6)***
CHILD PUGH SCORE	***Total N (%)***	***14 (27.4)***	***20 (34.5)***
A	***N (%)***	***8 (57)***	***17 (85)***
B	***N (%)***	***4 (28.6)***	***2 (10)***
C	***N (%)***	***2 (14)***	***1 (5)***

**only significant p-value in this table*

Endoscopy

The majority of oesophago-gastro-duodenoscopy (OGD) was done within office hours in the GI Unit's dedicated endoscopy suites (Control 92%, QIP 87.9%). The rest were done in an operating theatre either as it was after hours or due to unstable hemodynamics.

At OGD there was evidence of bleeding in Control 43.1% and QIP 55.1% of patients. Peptic ulcers were found most commonly (Control 43.1%, QIP 40.6%), followed by esophageal varices (Control 27.4%, QIP 34.5%) (Table 2). Antral or pre-pyloric lesions were found in 68% of ulcers in the control group and 47.8% in QIP group. Proton pump inhibitor was given to 35 (68.6%) and 33 (56.9%) prior to OGD in Control and QIP groups respectively. One patient in the Control group (1.9%) and two in QIP group (3.4%) with proven PUD did not receive PPIs pre or post-OGD. The two groups were statistically comparable regarding endoscopy findings. (Table 2)

Out of 12 bleeding ulcers (Forrest IA, IB and, IIA, IIB) 5 (41.6%) had dual therapy in the Control group versus 10 out of 14 (71%) in QIP group. One patient in the control group underwent a negative laparoscopy for suspected perforation. There were no operations performed for bleeding in the control group. Three in the QIP group had surgery after two failed attempts at endoscopic control using dual therapy. Surgery involved over-sewing of the bleeding vessel through an enterotomy and no resections were required. Repeat OGD was done on demand for 9 (17.6%) patients in the Control group and in 12 (20.6%) patients in QIP group. In the presence of blood in the upper GIT on OGD, the practice of dual endotherapy improved post implementation (p=0.023).

There were 14 (27.4%) and 21 (36.2%) patients with variceal bleeding in Control and QIP groups respectively. All oesophageal varices were managed with endoscopic banding whilst gastric varices were injected with Glue (histo-acryl). Varices occupying more than half the esophageal lumen were 57% Control and 45.5% QIP groups. All patients on Control arm were treated with Octreotide infusion whereas only 18 out of 21 patients (85.7%) in the QIP arm.

Table 2: Comparison of endoscopy findings and outcomes by groups

	CONTROL		QIP		P VALUE <0.05
ENDOSCOPY FINDINGS					
	N	(%)	N	(%)	
PEPTIC ULCER DISEASE	22	(43.1)	23	(39.6)	
ANTRAL / PRE-PYLORIC	15	(68.1)	11	(47.8)	
DUODENAL	6	(27.2)	11	(47.8)	
INCISURA	2	(9.0)	3	(13.0)	
BODY	0	(0)	2	(8.6)	
OESOPHAGEAL VARICES	14	(27.4)	19	(32.7)	
GASTRIC VARICES	2	(3.9)	2	(3.4)	
MALLORY WEISS	2	(3.9)	2	(3.4)	
VASCULAR MALFORMATION	0	(0)	2	(3.4)	
GASTRITIS	11	(21.5)	10	(17.2)	
OESOPHAGITIS	2	(3.9)	1	(1.7)	
GASTRIC CANCER	2	(3.9)	3	(5.1)	
POLYPS	1	(1.9)	0	(0)	
PUD FORREST CLASSIFICATION					
FORREST IA	1	(4.5)	3	(13.0)	
FORREST IB	3	(13.6)	6	(26.0)	
FORREST IIA	4	(18.1)	1	(4.3)	
FORREST IIB	4	(18.1)	3	(13.0)	
FORREST IIC	0	(0)	1	(4.3)	
FORREST III	10	(45.4)	9	(39.1)	
SECONDARY END POINTS					
FAILED PRIMARY ENDOSCOPY	9	(17.6)	12	(20.6)	
REQUIRED SURGERY	1	(1.9)	3	(5.1)	
30 DAY MORTALITY	5	(9.8)	6	(10.3)	

*some patients had more than one endoscopy finding, therefore will not add up to total PUD.

Table 3 details the difference in the comparator guideline parameters between the two groups. The QIP had a four hour greater time delay than the control but this was not statistically or clinically significant. Over 80% in both groups had their endoscopy within 24 hours (Control 83.7%, QIP 81.6%). Time to endoscopy was not statistically significantly different between the Control and QIP groups for low and high risk patients (suspected varices or MBS >10). However when both groups are combined, patients with a MBS of >10 or more had a statistically shorter 'Time to scope' by 8 hours than those with a score < 10 (p=0.02).

Blood transfusion was performed in (Control 72.5%, QIP 65.5%) (Table 1). The reason for transfusion was for resuscitation in 17.6% (Control) and 13.8% (QIP). The rest were transfused for clinical reasons. The mean Haemoglobin in stable patients who were transfused was statistically different between Control 6.3 (SD$\pm$2) and QIP 5.7 (SD$\pm$1.69) (p=0.04). The number of transfusions for HB above 7 was 12 (23.5%) (Control) to 6 (10.3%) (QIP) (p=0.047).

Table 3: QIP results

QIP Intervention parameters	*Control*	*QIP*	*P-Value*	*QIP success*	*Other audits*
Time to endoscopy (hours)		***Hours***			
Overall mean	17.8	22.9	0.9	No	
Varices mean	14.2	19.1	0.19	No	
MBS > 10	15.2	17.8		No	
		Percent			
Endoscopy within 24 hours	83.7	81.6	0.07		Canada 76% UK 69%
Dual endotherapy		***Number (Total)***			
With bleeding evidence on scope	5 (25)	14 (28)	0.02	Yes	France 29%
Inappropriate Blood transfusion		***Percent***			
Inappropriately transfused	23.5	10.3	0.047	Yes	

Morbidity

There was one major morbidity in the control group as a patient had a negative laparoscopy for a suspected perforation post endoscopy. After dual endoscopic therapy of an Antral high risk ulcer, the patient had localized peritonitis with free air seen under the diaphragm on an erect chest X-ray. At laparoscopy, there was no contamination of the peritoneal cavity and no ulcer visible. This patient recovered without further problems after surgery.

Mortality

There was one death directly related to bleeding in the QIP group. The mortality rate during the index admission was 5.9% (Control) and 1.72% (QIP).

Thirty- day mortality rate was 9.8% (Control) and 10.3% (QIP). This was not statistically different.

Univariate analysis showed that ‘unstable’ arrival hemodynamics (Grade III shock) was the only significant factor in determining 30 day mortality there was no statistical significant risks for mortality for age, haemoglobin, urea, Blatchford score, Time to endoscopy, endoscopy finding and presence of blood in GI tract.

Table 4: Univariate analysis for overall 30 days mortality

	P-VALUE
Grade III shock	0.009
Age	0.154
Admission Hb	0.49
Admission Urea	0.58
MBS	0.58
Bleeding	0.11
Scope finding	0.09
Time to endoscopy	0.75

Discussion

Societal and international guidelines for the management of UGIT are constantly being refined by senior gastroenterologists as evidence from RCT and cohort studies have accrued to provide sound evidence on which to base their recommendations. The international evidence based guideline contains 11 recommendations in six categories and details the criteria and cut-off levels when appropriate. These categories are: Adequate resuscitation, prognostic stratification, transfusion triggers, PPI acid suppression, early endoscopy and dual endotherapy.[5]

This study focused on three key aspects of UGIT bleeding care that we perceived form our current clinical practice required attention: Time to endoscopy, Use of dual endotherapy and a restrictive blood transfusion strategy for stable patients. These were the three aspects that were emphasized during our QIP implementation period.

All guidelines currently recommend early endoscopy (<24 hours) after admission.[9 11 5] After initial resuscitation patients are risk stratified into high risk and low risk groups. Risk stratification can be done using one of the validated pre-endoscopy scores like the MBS or Rockall pre-endoscopy score. The Modified Blatchford score is a pre-endoscopy tool that utilizes admission clinical and laboratory findings (systolic blood pressure, heart rate, Hb and urea). This score has been validated with other studies and correctly identifies the low risk patients A MBS of 0 and 1 has a less than 1% chance of needing intervention and these patients can be considered for outpatient management. Patients with MBS score of 10 or more are likely to need urgent intervention compared to patients with lower scores.[1 9] Patients with no signs of active bleeding and low risk should have their OGD within 24 hours of admission. High risk patients, MBS $\geq$ 10 and variceal bleeding, should preferably have their endoscopy within 12 hours. Patients with signs of ongoing bleeding should have an emergency OGD. In the literature, comparing very early (<12 hours) to late early (>12 hours) endoscopy, a meta-analysis found no significant reduction in re-bleeding, surgery or mortality.[12 13 14 15] Moreover, it was found that urgent endoscopy (0 to 8 hours) versus early endoscopy (6 or 8 to 24 hours),[14 16 17] did not show differences in clinical outcomes.[14 16]

Audits of registries show mostly below average uptake of guidelines. In the United Kingdom there was a 47.5% to 66% compliance to endoscopy within 24 hours in baseline audits.[9 10] Canadian RUGBE study showed a 76% 24 hour endoscopy rate.[2] With this background our finding of a more than 80% 24-hour endoscopy was pleasantly surprising. More than half were admitted after hours (Control 70.5%, QIP 58.6%) and despite this our Time to endoscopy was adequate. The QIP implementation didn't affect our within 24-hour endoscopy rate perhaps as our capacity to push for early scope is near the ceiling. The dedicated endoscopy unit is efficient and we capitalize on its excellent service during working hours. After hours endoscopy is challenging to arrange and also difficult to justify for stable patients as the emergency theatre is shared by all surgical disciplines. This also means that when we do have an emergency the operating theatre will go out of its way to accommodate us. This study also showed that overall patients with higher MBS had a shorter time to endoscopy on average by 8 hours. This implies that even before the QIP implementation patients were being risk stratified and triaged appropriately. The variceal group on average had a 3 hour shorter time to endoscopy than the overall group in both cohorts but this was not statistically significant.

Dual endotherapy use (or rather avoiding monotherapy with injection tamponade only) decreases the rate of re-bleeding and mortality. A large meta-analysis in 2004 showed that adding a second modality to injection tamponade decreased re-bleeding from 18.4% to 10.6% and mortality from 5.1% to 2.6%.[18] Despite this evidence a French audit in 2006 showed that 70.9% had injection therapy alone for high risk bleeding ulcers and mirrored our own institutions practice of a 100% monotherapy use for high risk ulcers reported by Levin et al between 2004 and 2009.[19 8] This QIP improved compliance to dual endotherapy modality. Our concurrent improvement in the availability of accessories for dual therapy at the time of the QIP most likely contributed to this improvement. The hesitation was with Forrest 2B (adherent clot ulcers) where only 25% had dual therapy. The literature on this is also divided between removing the clot and addressing the underlying lesion or using high dose IV PPI. This ambiguity in the guidelines reflects the lack of endotherapy in this group. A skilled endoscopist with a skilled assistant might attempt to tackle these clots as once stirred up to a third of them will resume bleeding.[20]

A restrictive blood transfusion strategy is applied to blood transfusion not only for UGIT but for several indications across many disciplines. In a patient that does not have ongoing bleeding, who is hemodynamically stable and does not have ischemic heart disease the recommended Hb trigger for transfusion is < 7g/dl.[21 11] A RCT in 2013 reported better mortality outcomes with this restrictive strategy in UGIT bleeding patients. [22] The subgroup that performed best was patients with variceal bleeding with Child-Pugh A and B. Re-bleeding and adverse effects were higher in the liberal strategy group. This QIP significantly reduced inappropriate over transfusions in our study from 23% to 10%.

The QIP failed to improve re-bleeding, surgery or mortality rates. The study is limited by the lack of sufficient patient numbers to see an effect on these secondary aims because of their relative infrequent occurrence. Our mortality rate of 9.8% and 10.3% resembles other quoted in international literature.[3 2 23] Levin et al's study done at our institution over 6 years looked at high grade bleeding ulcers only and had a mortality of 12.8%.[8] The mortality rate for equivalent Forrest categories Forrest IA to IIB in this much smaller cohort was 3.7% suggesting a trend towards improved in-hospital mortality over the past 8 years.

The mean Rockall score was 3.45 and 3.54 in Control and QIP groups respectively. Both were a medium risk and in Rockall et al's study, the re-bleeding rate was 14% and overall mortality rate of 5.3% for medium-risk patients. The second look endoscopy rate was 17 and 20% in this study, however, not all of these were bleeding at second OGD. The 30-day mortality rate of 9.8% and 10.3%in this study is higher than found for medium risk group in Rockall et al's study. However, in the subgroup that had re-bleeding the mortality rate was as high as 15% in this landmark paper.[3]

Presentation with shock was the only significant risk factor associated with mortality in this study. The initial hypotension and transient tissue hypoxia prior to resuscitation has far-reaching complications unfolding a cascade of organ function decompensation. Direct bleed related death was minor (one) and the rest of the deaths were due to medical co-morbidity. Could these deaths have been prevented by timely hospital presentation or recognition and triage in an overburdened community clinic? In centers that do not have endoscopy readily

available or enough emergency blood, the focus is on getting the patient to endoscopy. A burdened emergency center with even more burdened ambulance service results in delays in transfer and recognition of the hemodynamic decompensation.

Although our aim was not to look at pharmacotherapy directly, this study shows that the adherence to PPI for NVB and Octreotide for VB was good with both above 95%. We also did not audit a high dose versus low dose or oral PPI. In our context IV PPIs are available but with lack of evidence on definite reduction in surgery and mortality rates, we do not have access to high dose infusion use post endoscopy for high risk ulcers. The variceal bleeding protocol has been well established as we are a referral center. Up to 30% had variceal bleeding in this study. All patients received Octreotide and antibiotics. There is currently an ongoing detailed audit regarding VB management in our hospital.

The NICE QIP audit in 2012/2013 highlighted the need for educating clinicians on a regular and repeated basis to ensure guideline adherence. It is not merely sufficient to have many complex guidelines if this does not reach the day to day practice. Quality audits and improvements based on these audits together with continuous education of clinicians can result in better patient care. Unit protocols with standardized admission forms asking pertinent questions like risk stratification and check list of therapy needed can aid clinicians in better management of UGIT bleeding.

This study has provided us with benchmarks values for adherences for three key guideline recommendation in the management of UGIT. We have shown in this study over a period of two years that our compliance with time to endoscopy of less than 24 hours at 80% is very good and above those reported in high income countries. Similarly adherence to PPI and Octreotide was above our expectations. Our QIP improved compliance with the delivery of dual therapy and adherence to transfusion triggers. Effects on the need for surgery and mortality which are in the middle of the ranges of recent reports are difficult to interpret and require multi center studies with much larger numbers to prove any effect of guideline adherence.

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STUDY APPROVAL DOCUMENTATION

3.1 Human Research Ethics Committee

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

18 April 2017

HREC REF: 244/2017

Dr J Klopper
Department of Surgery
OMB

Dear Dr Klopper

PROJECT TITLE: UGIT BLEED: A COMPARATIVE OUTCOMES STUDY OF PRE AND POST IMPLEMENTATION OF MANAGEMENT GUIDELINES IN THE ACUTE CARE SURGERY UNIT, GROOTE SCHUUR HOSPITAL (MMed-candidate-Dr I Aborkis) sub-study linked to R034/2016

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 April 2018.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

The HREC acknowledge that the student, Dr Ismail Aborkis will also be involved in this study.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

HREC 244/2017

3.2 Annual Progress/Renewal Report

UNIVERSITY OF CAPE TOWN
IYUNIVESITHI YASEKAPA • UNIVERSITEIT VAN KAAPSTAD

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30/11/2019
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	1/12/2018

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	30/11/2018		
HREC REF Number	244/2017	Current Ethics Approval was granted until	
Protocol title	UGIT Bleed: A Comparative Outcomes Study Of Pre And Post Implementation Of Management Guidelines In The Acute Care Surgery Unit, Groote Schuur Hospital (MMed-Candidate-Dr I Aborkis) Sub-Study Linked To R034/2016		
Principal Investigator	Dr S Rayamajhi		
Department / Office Internal Mail Address	General Surgery, J Floor, OMB		
1.1 Does this protocol receive US Federal funding?		☐ Yes	X☐ No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
☐X	Data collection is complete, data analysis only
Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.	

HUMAN RESEARCH ETHICS COMMITTEE
30 NOV 2018
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		56
Total number of records or specimens collected, reviewed or stored since last progress report		108
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐ Yes	☒ No

4. Signature

Signature of PI	PP	Date	30/11/2018

3.3 Study protocol

UGIT bleed: A comparative outcomes study of pre and post implementation of management guidelines in the Acute Care Surgery Unit, Groote Schuur Hospital

Principal investigators:
Dr. Shreya Rayamajhi MBChB (UFS), FCS(SA)
Consultant, Acute care surgery, GSH

Dr. Ismail Aborkis MBChB, FCS (SA).
MMed candidate
Registrar, General surgery, UCT

Research methodology and statistical analysis
Dr. Richard Spence MBChB (UCT), MPhil (CAM), Ph.D. (UCT).
Registrar, General surgery, UCT.

Dr. Juan Klopper MBChB (UFS), FCS (SA), MMed (UFS).
Head of the unit, Acute care surgery, GSH

Mentors:
Prof. Sandie Thomson ChM, FRCS (Ed & Eng) FRCP (Ed)
MWGO HOD, Medical GIT, UCT, GSH

Prof. Eugenio Panieri MBChB (UCT), FCS (SA).
Head o of Surgery, secondary level hospitals, Cape Metro-West

Prof. Del Kahn MBChB, CRM, FCS (SA).
Head of General Surgery, UCT, GSH

Acknowledgment: **Prof. Kathryn Chu** from the Department Research Committee for suggesting that we do a post-implementation study rather than an audit which was previously submitted to the DRC
Correspondence: shreya.r@hotmail.com

PROTOCOL SYNOPSIS

Title

UGIT bleed: A comparative outcomes study of pre and post-implementation of management guidelines in the Acute Care Surgery Unit, Groote Schuur Hospital.

Study center

Acute Care Surgery Unit, Groote Schuur Hospital, Cape Town, South Africa

Study period

Retrospective historical control: 01-01-2016 to 31-12-2016

Intervention time: Jan 2017

Prospective Cohort: 01-02-2017 to 31-01-2018

Objectives

Primary:

- Efficacy of our intervention at ensuring optimal endoscopic management of UGIT bleed specifically looking at the time to endoscopy and modality used to arrest hemorrhage.
- Mortality and bleed related morbidity comparison pre and post implementation
- Adherence to international consensus guideline for blood transfusion outside of resuscitation in the presence of UGIT bleed.

Secondary:

- Audit of ACS, GSH emergency endoscopy practice
- Audit of ACS blood transfusion practice for UGIT bleed
- Audit of ACS mortality and morbidity for UGIT bleed
- Audit of re-bleeding and adjuncts to endoscopy used to arrest bleeding.

- **Design**

Comparative study between a historical control group vs prospective cohort post implementation of a quality improvement intervention. The Management of UGIT at GSH guidelines will be strongly implemented as part of the intervention.

Methodology

Population:

All patients admitted to the ACS unit a documented UGIT bleed over the time period will be included.

The exclusion criteria include:

- An Upper endoscopy shows no stigmata of a bleed or causes for an upper GIT bleed
- Patients deemed stable enough to discharge by Emergency unit with a suspected GI bleed, i.e. Patients not admitted to ACS

Intervention:

We have identified the general surgical registrars, the consultants covering Acute Care Surgery and the Medical GI fellows doing endoscopy calls as our target intervention population. The Cape metro-west GI bleed protocol and the GSH Upper GIT bleed guidelines are present but not actively implemented. The timing of the endoscopy especially after-hours and the treatment modality is up to the knowledge and clinical discretion of the team on call. The registrars rotating through ACS are in their 2nd or 3rd year training. The endoscopy consultant is either the Acute Care Surgery consultant on-call or a medical GIT fellow, both deemed competent by the Unit heads.

The intervention will include the following:

1. Dissemination of all relevant protocols and guidelines to the target group via email. These are:
    - Upper GI bleed protocol for Cape Metro-west as written by Prof. E. Panieri and Prof. S. Thomson
    - GSH ACS UGIT bleed guidelines as written by Prof. E. Jonas and Dr. S. Rayamajhi
    - Data we aim to capture with this study, to ensure they take a relevant history and document it inpatient notes

2. A discussion forum with this target group where we will introduce the protocol of this study, discuss key points and have a Q&A session to answer their concerns about this study. This meeting will ideally be done the beginning of 2017(January) pending the results of the DRC.
3. Poster of management algorithm will be put up in the emergency department, E23 endoscopy unit and F25 Acute Care ward.
4. With each new group of rotating Acute care registrars (6 registrars at a time, rotate 3 monthly), we will hold an information session again to re-enforce the guidelines.

The aim of the intervention will be to enforce the following:

- Early endoscopy:
    1. Unstable hemodynamics – ASAP or within 2hours of arrival.
    2. Stable or well resuscitated –suspected variceal bleeds within 12 hours, suspected non-variceal bleed with Modified Blatchford Score (MBS) >10 within 6 hours, MBS <10 within 24 hours
- Dual therapy for ulcer bleeds
- Blood transfusion to Hemoglobin of 7mg/dl for patients without Ischemic Heart Disease, Hb of 9mg/dl for patients with IHD (out of resuscitation).

Data collected

We aim to collect the following data. The database has been approved by the Human Research Ethics Committee of UCT, reference no R034/ 2016.

Variable	Option	Rationale
Hospital number		
Demographics		Does the burden of disease correlate with international studies or are our patients younger as is the impression
Age	Numerical	
Gender	M/F	
Presentation		
Current inpatient	Yes / No	Is mortality higher in patients that bleed as an inpatient while admitted for other causes and not an UGITB
Transfer from	NSH/MPH/VHW/None	Is there mortality and morbidity related to Transfer
Reason for transfer	No afterhours scope/ No scope adjuncts	Identify pitfalls to address in secondary hospitals
First presentation to hospital	Time	
Presentation after hours	Yes / No	Is there an increased mortality or morbidity risk Is there an increased delay to endoscopy
Presentation status		To risk stratify into High and low risk (MBS)
Hemodynamics at presentation	Stable / Unstable	
Systolic BP		
Heart rate		
Admission Hemoglobin (lab)		

Admission Blood Urea		
Melena	History / Confirmed / None	
Hematemesis	History / Confirmed / None	
Syncope	Yes / No	
Resuscitation	Fluids / Blood / Inotropes / None	
Risk factors for Peptic ulcer disease /bleeding		To identify the burden of PUD from Smoking and NSAID use in the South African setting
Smoking	Daily / Occasionally / Never	
NSAIDs	Occasional / Regular / None	
Aspirin	Yes / No	
Aspirin dose	Prophylactic / Analgesic	
Previous UGITB	Yes / No	
Warfarin	Yes / No	
Co-morbid diseases (on history or active)		To enable risk stratification according to internationally validated Rockall score
Ischemic heart disease	Yes / No	
Cardiac failure	Yes / No	
Chronic renal failure	Yes / No	
Liver disease/ failure	Yes / No	
Modified Blatchford Score	Numerical	
Endoscopy findings		
Time to endoscopy	In hours	
Scope location	GI unit / Theater	
Bleeding evidence on Scope	No blood / Fresh blood / Old blood	
Scope findings	Esophageal varices / Gastric varices / PUD / Mallory Weiss tear / Vascular malformation	
Esophageal varices	Active bleed / Not bleeding	
Varices grade	Occupy more than half the lumen / Occupy less than half the lumen	

Endoscopy therapy		What is our practice and has our intervention changed it
Varices therapy	Bands / Sengstaken /Sclerotherapy	
Number of Bands		
Variceal adjuncts	TIPPS / Surgery	
PUD forrest classification	Forrest classification	
Ulcer site	Duodenal / Antral or pre-pyloric / Incisura / Gastric Body	
Ulcer endotherapy	Injection / Clip / Thermal	
Ulcer dual therapy	Yes / No	
Monotherapy reasons	Adjuncts unavailable / Adjuncts malfunction / Lack of skills	Identify pitfalls
Bleeding controlled after endotherapy	Yes / No	
Total no of endoscopy		
Intervention radiology	Yes / No	
Surgery	Yes / No	
Surgical management	Vessel oversewn / distal gastrectomy / total Gastrectomy	
Bleeding stopped after Surgery or Intervention radiology	Yes /No	
Rockall score	Numerical	
Child-Pugh score	A /B/ C	Grade severity of liver disease/ cirrhosis
Blood transfusion practice		Do we follow consensus guidelines for transfusion outside of a resuscitation Scenario
Blood transfusion	Yes / No	
Hemoglobin prior to transfusion for low Hb only (lab)		
Transfusion purpose	Resuscitation / Low Hb	
Morbidity		

Complications	Yes / No	
Complication post-operative	Wound / Pulmonary / Intra-abdominal	
Grade worst complication	Clavien Dindo classification	
Complication other		
Death	Yes /No	
Death bleeding related	Yes / No	
Hospital stay		
Length of stay	Days	
Length of ICU stay		

Data management

Data will be captured using a red cap online form. Only the principal investigators will have access to this online database which is password controlled and firewall- protected. The excel spreadsheet that is exported from the red cap for analysis will be stored in the principal investigators computer which is password controlled.

Statistical analysis

Continuous variables that are normally distributed will be compared using parametric analysis. Categorical variables and skewed data will be compared using non-parametric methods. Sample size will be determined by the accrual of patients during the study period, which is estimated to be approximately 200 patients. This will power the study to 90% to demonstrate a proportional difference between the pre and post-intervention cohorts of 20% ($p<0.05$).

Ethics

Ethics for the database has already been approved. R244/2017 HREC. As discussed with HREC for the prospective data collection we will obtain verbal consent from the patients. This will be documented in the patient notes. Patients will be informed that their management will not alter and we are collecting data for study purposes.

Ethics for the study will be obtained from the Faculty of Health Sciences UCT Human Research Ethics Committee University of Cape Town.

Only the hospital number will be used to identify the patient, no use of names or address is necessary.

Publication

We aim to publish the study in a peer-reviewed Journal. The South African experience and outcomes can be compared to international publications. The efficacy of the intervention will be of interest to the Surgical and GIT community at large.

Budget

The stationery and posters will be financed by the principal investigators.

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4. ADDENDUM

4.1 **Table1**: Pre-Endoscopy Rockall Score

For risk of re-bleeding and death After Admission to the Hospital for Acute UGI bleeding

Variable	**Score 0**	**Score 1**	**Score 2**	**Score 3**
Age (years)	< 60	60-79	>80	
Comorbidity	Nil major		Congestive heart failure, Ischaemic heart disease	Renal failure, Liver disease, metastatic cancer
Shock	No shock	Pulse >100 bpm	Systolic BP >100	
Bleeding source	Mallory-Weiss tear	All other diagnosis: e.g., esophagitis, gastritis, peptic ulcer disease, varices	Malignancy	
Features of recent bleeding	None		Adherent clot, spurting vessel	

4.2 Table 2: Modified Glasgow-Blatchford Score (MBS), pre endoscopy assessment

Risk factors	Score
Blood urea (mmol/L)	
>6.5 to <8	2
>8 to <10	3
>10 to <25	4
>25	6
Hemoglobin (g/dL), for men	
>12.0 to <13.0	1
>10.0 to <12.0	3
<10.0	6
Hemoglobin (g/dL), for women	
>10.0 to <12.0	1
<10.0	6
Systolic blood pressure (mmHg)	
100-109	1
90-99	2
<90	3
Pulse rate per minute	
>100	1
Maximum score	16

4.3 Table 3: AIMS65 scoring system

AIMS65 Score	
Variable	Score
Age >65	1
Systolic BP <90	1
Altered mental status	1
Albumin <3g/L	1
INR >1.5	1
Maximum score	5
Scores >2 are considered high risk	

4.4 Table 4: Forrest classification of upper gastrointestinal hemorrhage

Stage	Description
Acute hemorrhage	
Forrest IA	Active spurting hemorrhage
Forrest IB	Oozing hemorrhage
Signs of recent hemorrhage	
Forrest IIA	None bleeding visible vessel
Forrest IIB	Adherent clot
Forrest IIC	Dark base/ haematin covered
Lesion	
Lesion without active bleeding	
Forrest III	Clean-base ulcer

4.5 Table 5: Child-Turcotte-Pugh Classification for Severity of Liver Cirrhosis

Parameter	1 Point	2 Points	3 Points
Ascites	None	Mild-moderate	Sever
Encephalopathy	None		Minimal
Advanced (coma)			
Albumin (g/L)	<35	35-28	<28
Bilirubin (mmol/L)	<34	34-50	>50
INR	<1.7	1.7-2.3	>2.3

AWARENESS POSTER

UPPER GASTROINTESTINAL BLEEDING QUALITY IMPROVEMENT PROGRAM

GSH ACUTE CARE SURGERY AND MEDICAL GIT UNIT

AIM: PROMOTE ADHERENCE TO UGIT BLEEDING GUIDELINE RECOMMENDATIONS

WHAT ARE THE GUIDELINE RECOMMENDATIONS?

ENDOSCOPY TIMING

- **UNSTABLE**: ASAP (<2 hours)
- Stable with **MBS ≥ 10**: <12 hours
- Stable with **MBS < 10**: <24 hours
- Stable suspected **variceal** bleed: <12

ENDOTHERAPY

Dual modality for FORREST I and II ulcers

TRANSFUSION TRIGGER

Active bleed - as necessary until hemostasis

Out of resuscitation (Top up):

- No Ischemic heart disease – Hb ≥ 7.0 g/dL
- Ischemic heart disease – Hb ≥ 9.0 g/dL

REQUIRED INFORMATION

MODIFIED BLATCHFORD SCORE (MBS)	
Blood urea (mmol/L)	
≥6.5 <8.0	2
≥8.0 <10	3
≥10.0 <25	4
≥25	6
Hemoglobin (g/dL) for men	
≥12.0 <13.0	1
≥10.0 <12.0	3
<10.0	6
Hemoglobin (g/dL) for women	
≥10.0 <12.0	1
<10.0	6
Systolic blood pressure (mmHg)	
100-109	1
90-99	2
<90	3
Pulse rate per minute	
>100	1

Data will be prospectively collected for a year from February 2017

For the comparative QIP study (HREC 244/2017)

Principal investigator: Dr Ismail Aborkis, Department of General Surgery, GSH